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# *Helicobacter pylori* eradication in dyspeptic primary care patients: a randomized controlled trial of a pharmacy intervention

**ABSTRACT** ● **Objective** To determine the effectiveness of structured adherence counseling by pharmacists on the eradication of *Helicobacter pylori* when using a standard drug treatment regimen. ● **Design** Randomized controlled clinical trial. ● **Setting** Nonprofit group-practice health maintenance organization (HMO). ● **Participants** HMO primary care providers referred 1,393 adult dyspeptic patients for carbon 14 urea breath testing (UBT). ● **Interventions** Those whose tests were positive for *H pylori* (23.3%) were provided a standard antibiotic regimen and randomly assigned to receive either usual-care counseling from a pharmacist or a longer adherence counseling session and a follow-up phone call from the pharmacist during drug treatment. All subjects were given the same 7-day course of omeprazole, bismuth subsalicylate, metronidazole, and tetracycline hydrochloride (OBMT). Dyspepsia symptoms were recorded at baseline and following therapy. ● **Outcomes** The main outcome was eradication of *H pylori* as measured by UBT at 3-month follow-up. Secondary outcomes were patient satisfaction and dyspepsia symptoms at 3-month follow-up. ● **Results** Of the 333 participants randomly assigned to treatment, 90.7% completed the 3-month follow-up UBT and questionnaires. Overall eradication rate with the OBMT regimen was 80.5% with no significant difference in eradication rates between the 2 groups ( $P=0.98$ ). ● **Conclusions** In this study, additional counseling by pharmacists did not affect self-reported adherence to the treatment regimen, eradication rates, or dyspepsia symptoms but did increase patient satisfaction.

A clear association exists between *Helicobacter pylori* and peptic ulcer disease,<sup>1,2</sup> gastritis,<sup>3</sup> and mucosa-associated lymphoid type lymphoma.<sup>4</sup> Current clinical care guidelines call for antibiotic treatment when *H pylori* infection is confirmed in those with a current or past ulcer or lymphoma.<sup>5-7</sup> However, treating *H pylori* in patients with

nonulcer dyspepsia is still a debated question.<sup>8-13</sup> Various theoretic models of practice strategies have been developed.<sup>14-16</sup> Key issues affecting the conclusions of these clinical treatment models include *H pylori* prevalence, medication compliance, treatment effectiveness, the nature of the relationship between *H pylori* and dyspepsia,

### Summary points

- *Helicobacter pylori* was not as prevalent in this sample of patients with dyspepsia as in dyspeptic patients in other recent studies
- A reasonable eradication rate was achieved with the use of pharmaceutical treatment (omeprazole, bismuth subsalicylate, metronidazole, and tetracycline hydrochloride)
- Special added counseling by pharmacists did not affect eradication rates in this sample
- *H pylori* eradication did not affect symptoms of dyspepsia

and the prevalence of peptic ulcer disease within the dyspeptic population.<sup>7-10,14,15</sup> In this uncertain situation, there is concern that some clinicians are routinely treating *H pylori* infections (or presumed infections) in many patients with uncomplicated dyspepsia despite the lack of evidence of a causative relationship or improved outcome following therapy.<sup>8,10,11</sup>

Treatment strategies for *H pylori* used in primary care and gastroenterology are frequently different.<sup>11,17</sup> Prospective studies on this subject have involved mostly patients referred to subspecialty care.<sup>8-10</sup> This has allowed for endoscopy as a baseline to exclude ulcer disease and define a patient as having nonulcer dyspepsia, but this is not how most dyspepsia is managed and treated in clinical practice.<sup>11</sup>

We conducted a randomized, controlled trial to determine the effect of adherence counseling on the eradication of *H pylori* in primary care patients with dyspepsia using a standard drug regimen. We hypothesized that more intensive counseling from pharmacists would improve patient adherence to the four-drug treatment regimen and thereby improve the eradication of *H pylori* and maximize the treatment effect. Secondary hypotheses were that added counseling by pharmacists would result in greater patient satisfaction and reduced symptoms following treatment.

## PATIENTS AND METHODS

### Setting

The study was conducted in a prepaid, closed-panel health maintenance organization (HMO) providing comprehensive medical care, including pharmacy, to more than 430,000 members in the Portland, Oregon, metropolitan area. Although the race of participants in this study was not recorded, the general population of this HMO's patients is 87% white and English-speaking. This study was reviewed and approved by our institutional review board.

### Recruitment

Recruitment occurred between June 1997 and December 1998 and included the referral of dyspeptic patients by primary care providers, supplemented by the use of an automated records system that identified patients aged 18 or older who had been diagnosed with dyspepsia and who had a history of medication use for dyspepsia (histamine-2-receptor blocker antagonists [H2RA]). For the purpose of this study, dyspepsia was defined as a chronic upper abdominal pain, with or without relation to meals, for which no clear cause has been established, as evaluated by primary care professionals.<sup>18-20</sup> Referrals included patients with dyspepsia for longer than 4 weeks but excluded those with symptoms limited to gastroesophageal reflux disease, irritable bowel syndrome, cholelithiasis, and angina. Patients were also excluded if they were pregnant or trying to conceive, had cancer diagnosed in the past 2 years, had been hospitalized within a month of recruitment, or had a known sensitivity to the study drugs.

Potential participants were sent a study description and were then called by a recruiter who confirmed interest and eligibility. Those who agreed to screening were scheduled for an *H pylori* test and sent a copy of the consent form. At the time of the test, potential participants were met by a project staff member, given an opportunity to ask any questions, and then asked to sign the consent form. Participants then completed a baseline symptom questionnaire and an *H pylori* test.

An additional 11 patients with dyspepsia were referred by gastroenterologists. These patients had tested positive for *H pylori* on the rapid urease test for *Campylobacter*-like organism performed during endoscopy. These patients signed the informed consent form and completed the study questionnaires but did not have the baseline urea breath test (UBT) because the presence of *H pylori* had already been confirmed.

### Measurement

All participants completed a symptom questionnaire rating the intensity of dyspepsia, heartburn, nausea, constipation, and diarrhea. The dyspepsia question was, "During the past 30 days, have you been bothered by stomach aches or pains? Stomach ache refers to all kinds of aches or pains in your stomach or belly," with a graded scale of none, mild, moderate, or severe. Additional questions were asked on general health, pain interfering with usual daily activity (not at all, little bit, moderate, quite a bit, and extreme), and satisfaction with pharmacy services, "How satisfied were you with the pharmacy services you received for your stomach problem (very satisfied, satisfied, dissatisfied, very dissatisfied)?"

Testing for *H pylori* was done using a carbon 14 UBT (Pytest; Tri-Med Specialties, Inc, Charlottesville, VA). To

ensure an accurate test result, potential participants were screened, by phone and at the time of testing, for any antibiotic or bismuth use in the previous month, use of proton-pump inhibitors or sucralfate in the past 14 days, or use of H2RAs or antacids in the past 24 hours. This commonly used diagnostic test has a sensitivity of 97% and a specificity of 100%.<sup>21-23</sup> Breath samples were collected in a Mylar balloon according to the manufacturer's protocol. Values were reported as positive if greater than 200 disintegrations per minute occurred.

The primary outcome measure was eradication of *H pylori*, as measured by a UBT at the 3-month follow-up. Secondary outcome measures included symptoms as reported on the symptom questionnaire and satisfaction with treatment.

### Drug treatment

Treatment consisted of a 7-day regimen of omeprazole, 20 mg daily; bismuth subsalicylate, 2 tablets 4 times a day with food; metronidazole, 250 mg 4 times a day with food; and tetracycline hydrochloride, 500 mg 4 times a day with food. This regimen is referred to as OBMT. These drugs were provided in a blister pack with each day's dose clearly indicated.

### Randomization

Participants who tested positive for *H pylori* were randomly assigned to either usual care or special counseling using a computer-generated random sequence. The participating pharmacies were provided with a supply of opaque randomization envelopes, and the pharmacists were trained to open the top envelope to determine the treatment assignment for each new research participant.

### Treatments

Patients in both groups received the same OBMT medication regimen. In the usual pharmacy care condition, patients met for 5 minutes with the dispensing pharmacist. The pharmacist described the proper protocol for taking the prescribed drugs, and the patients had the opportunity to ask questions. This procedure is consistent with the current standard of pharmacy practice for dispensing these drugs.

Participants assigned to the special intervention received a 15-minute counseling session with the pharmacist, including a detailed review of possible side effects, emphasis on the importance of completing the entire drug regimen, discussion about possible barriers to adherence and coping strategies, and encouragement to call the pharmacist in the event of any problems. In addition to this extended counseling session, the pharmacist also scheduled a follow-up telephone call with the patient 2

to 3 days after the start of therapy to check on adherence to the drug regimen. All of the participating pharmacists received a special 4-hour training session in counseling techniques.

### Follow-up data collection

Participants in both groups were contacted by telephone 8 days after they started the medication regimen and were asked to report their adherence to the regimen and their current symptoms. All participants were contacted again 90 days after receiving the treatment drugs and asked to complete a second UBT and the symptom questionnaire. All data collectors were masked to treatment assignments.

### Analyses and power calculation

Statistical analyses were conducted using statistical software (Statistical Analysis Software, version 6.12; SAS Institute, Inc, Cary, NC). Participants with missing follow-up data were not included in the analyses of follow-up data. The intended sample size for the study was 150 participants per treatment. This sample size would have been sufficient to detect a difference in eradication rates between treatments of 0.80 versus 0.65, with a *P* of 0.05 and a power of 90%. Given the cost of providing added counseling by pharmacists, we determined that this level of difference in eradication rates would be required to justify changing current practice patterns.

## RESULTS

Of the 2,321 patients contacted, 438 were not interested in participating, 211 were found during the telephone interview to be ineligible, 1,672 were enrolled, and 1,393 underwent UBT. Of these, 325 (23.3%) were found to be positive for *H pylori* and were randomly allocated into the

Table 1 *Helicobacter pylori* prevalence in study subjects, by age and sex

Age categories, yr	Subjects, no.	Positive UBT, %
<b>Men</b>		
18-44	209	21.1
45-64	277	24.9
≥65	111	34.2
All ages (total)	597	25.3
<b>Women</b>		
1-44	304	17.4
45-64	360	22.2
≥65	132	31.1
All ages (total)	796	21.9
<b>All participants</b>	<b>1,393</b>	<b>23.3</b>

UBT = urea breath test.

study (see this article on our website for a chart showing participant flow through the study). Greater prevalence was seen in the older participants, but there was not a significant difference in prevalence between men and women (table 1).

Patient self-reports of medication adherence at the 8-day follow-up were similar in both treatment arms. The percentage of participants missing one or more doses of each component of the OBMt regimen, respectively, were 7.7%, 17.2%, 15.0%, and 16.6% for the usual-care group, and 4.9%, 12.2%, 11.0%, and 12.2% for the special-intervention group.

Of the 333 randomly allocated participants, follow-up UBTs were done on 302 (90.7%) at the 90-day follow-up. The eradication rate did not differ by treatment condition (table 2). The brief-counseling control group had an eradication rate of 80.5% versus the special-counseling group's rate of 80.4% ( $\chi^2 = 0.001$ ,  $P = 0.98$ ). Although the special counseling did not increase the eradication rate, it resulted in significantly higher satisfaction with the pharmacy services, with 94.6% of the special-counseling group reporting "very satisfied" versus 77.2% in the control condition ( $\chi^2 = 18.82$ ,  $P < 0.001$ ) (table 3).

When both treatment groups were combined and those for whom eradication was achieved were compared with those still testing positive for *H pylori*, no differences were found in symptoms reported at 90 days. For example, the proportions of participants reporting no stomach pain at 90 days were 55.9% for those testing positive and 51.7% for those testing negative (table 4). No differences were seen for other symptoms, including heartburn, nausea, constipation, and diarrhea (data not shown). Similarly, there was no difference in the reporting of stomach pain interfering with usual daily activities in the past 4 weeks, at the time of the 3-month follow-up (see table 4).

Table 2 Helicobacter pylori eradication at 90 days in study subjects, by intervention, sex, and age

Variable	Subjects, no.	Percentage
<b>By intervention</b>		
Usual care control*	154	80.5
Special treatment	148	80.4
<b>By sex</b>		
Men†	140	83.6
Women†	162	77.8
<b>By age, yr</b>		
18-29†	16	75.0
30-45†	78	73.1
46-64†	139	80.6
≥65†	69	89.9

\* $\chi^2 = 0.001$ ,  $P = 0.98$ .

†Usual-care control and special-treatment groups combined.

Table 3 Percentage of patients satisfied with pharmacy service as reported at 90-day follow-up\*

Study group	Subjects, no.	Very satisfied, %	Satisfied, %	Dissatisfied, %
Control	149	77.2	20.8	2.0
Special treatment	147	94.6	5.4	0

\* $\chi^2 = 18.82$ ,  $P < 0.001$ .

## DISCUSSION

The prevalence of *H pylori* in our dyspeptic population was lower than expected. Worldwide, *H pylori* prevalence in the general population ranges from less than 15% to more than 80%, with the prevalence in the United States somewhat lower than in most countries studied.<sup>24</sup> In a study of asymptomatic persons in Houston, Texas, the overall prevalence was 52%, with a lower prevalence in whites than in minorities.<sup>25</sup> We expected that the prevalence of *H pylori* in our population of dyspeptic patients would be higher than that in the general population and were surprised to find a prevalence of only 23.3%. This comparatively low prevalence may reflect differences between our primary care population and the subspecialty populations of other studies. Our findings that the prevalence was the same in men and women and that prevalence was higher in older patients are consistent with those of other studies.<sup>24,25</sup>

The definition of dyspepsia has varied, with some studies on nonulcer dyspepsia focusing on more severe symptoms and using endoscopy as a baseline to exclude patients with ulcers.<sup>8-10,19</sup> Three recent prospective studies on the relationship between symptoms and eradication used a patient pool from subspecialty care.<sup>8-10</sup> In contrast, primary care physicians see a wide spectrum of patients with

Table 4 Subjects continuing to report stomach pain (dyspepsia)

Pain reported at 90-day follow-up, %*†						
<i>H pylori</i> status	Subjects, no.	None	Mild	Moderate	Severe	
Positive	59	55.9	22.0	17.0	5.1	
Negative	242	51.7	23.1	16.9	8.3	
Stomach pain reported to interfere with usual daily activities, %‡						
<i>H pylori</i> status	Subjects, no.	Not at all	Little bit	Moderate	Quite a bit	Extreme
Positive	59	35.6	22.0	17.0	17.0	8.4
Negative	240	45.4	24.6	13.8	11.2	5.0

\*"During the past 3 months following the 1-week treatment for your stomach problem, have you been bothered by stomach aches or pains: (Stomach ache refers to all kinds of aches or pains in your stomach or belly.)"

† $\chi^2 = 0.818$ ,  $P = 0.85$ .

‡ $\chi^2 = 3.765$ ,  $P = 0.44$ .

dyspepsia and do not always have access to endoscopy. Our participants were from a single community, with more than 95% from primary care practice. Although a few patients with undetected ulcers may have been included in our study, the inclusion of patients with ulcers would have increased the chances of a positive symptom response to *H pylori* eradication.<sup>8,26,27</sup>

The addition of special counseling by the pharmacy increased satisfaction with service, but it did not improve self-reported medication adherence or eradication rate. Even with the different pharmacy interventions, it is clear that our study population was highly motivated. More than 90% of the randomly allocated patients completed the study. Our participant selection procedures may have had the effect of screening out those who were at highest risk of poor medication adherence. Another limitation of our study is that the same pharmacists delivered both interventions and, therefore, may have mixed some elements of the counseling treatments. Occasional observation checks for quality control did not show evidence of this problem, but some contamination between treatments cannot be ruled out. Also, the use of the blister packs for dispensing medicines may have also increased compliance in both groups.

The eradication rate of 80.5% with this drug combination (OBMT) was consistent with the use of OBMT in other settings.<sup>28</sup> Also consistent with other studies was the same eradication rate for men and women.<sup>3,25</sup> However, there was a trend toward greater eradication in the older age groups.

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